Chronic bacterial prostatitis and chronic pelvic pain syndrome

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ABSTRACT

INTRODUCTION: Chronic prostatitis can cause pain and urinary symptoms, and can occur either with an active infection (chronic bacterial prostatitis [CBP]) or with only pain and no evidence of bacterial causation (chronic pelvic pain syndrome [CPPS]). Bacterial prostatitis is characterised by recurrent urinary tract infections or infection in the prostate with the same bacterial strain, which often results from urinary tract instrumentation. However, the cause and natural history of CPPS are unknown and not associated with active infection. METHODS AND OUTCOMES: We conducted a systematic overview and aimed to answer the following clinical questions: What are the effects of treatments for chronic bacterial prostatitis? What are the effects of treatments for chronic pelvic pain syndrome? We searched: Medline, Embase, The Cochrane Library, and other important databases up to February 2014 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 131 studies. After deduplication and removal of conference abstracts, 67 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 51 studies and the further review of 16 full publications. Of the 16 full articles evaluated, three systematic reviews and one RCT were included at this update. We performed a GRADE evaluation for 14 PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for 12 interventions based on information relating to the effectiveness and safety of 5 alpha-reductase inhibitors, allopurinol, alpha-blockers, local injections of antimicrobial drugs, mepartricin, non-steroidal anti-inflammatory drugs (NSAIDs), oral antimicrobial drugs, pentosan polysulfate, quercetin, sitz baths, transurethral microwave thermotherapy (TUMT), and transurethral resection of the prostate (TURP).

QUESTIONS

INTERVENTIONS

Footnote

* No RCTs; categorised on the basis of consensus and non-RCT evidence

Key points

- Chronic prostatitis is a syndrome of pain and urinary symptoms, and occurs either with recurrent bacterial infection (chronic bacterial prostatitis [CBP]) or as pain without evidence of bacterial infection (chronic pelvic pain syndrome [CPPS]). Occasionally, there may be positive bacterial cultures from prostatic secretions in CPPS, but no evidence that these are causative of the men's symptoms.

  Bacterial infection can result from urinary tract instrumentation, but the cause and natural history of CPPS are unknown.

- Chronic bacterial prostatitis has identifiable virulent micro-organisms in prostatic secretions.

  Oral antimicrobial drugs are beneficial for CBP, although trials comparing them with placebo or no treatment have not been found.

  Clinical success rates with oral antimicrobials have reached about 70% to 90% at 6 months in studies comparing different regimens.

  Trimethoprim and quinolones are most commonly used. These should be used above other antibiotics given their ability to penetrate the prostate, except in circumstances where specific bacterial sensitivities indicate otherwise.

  Although we don't know from clinical trials whether local injections of antimicrobial drugs or transurethral resection of the prostate improve symptoms compared with no treatment in people with CBP, these should be considered for those that fail oral antibiotics.

- Effective treatment regimens for chronic pelvic pain syndrome remain to be defined, and strategies are based on symptomatic control and anxiety relief.

  Alpha-blockers have been found in some RCTs to have some efficacy in symptom relief of CPPS; however, there are studies that show no effect. To date, we don't know how effective alpha-blockers are in people with CPPS.

  We don't know whether 5 alpha-reductase inhibitors, NSAIDs, pentosan polysulfate, allopurinol, transurethral microwave thermotherapy, sitz baths, mepartricin, or quercetin reduce symptoms in men with CPPS.

Clinical context

GENERAL BACKGROUND

Chronic prostatitis can cause pain and urinary symptoms, and can occur either with an active infection (chronic bacterial prostatitis [CBP]) or with only pain and no evidence of bacterial causation (chronic pelvic pain syndrome [CPPS]). Bacterial prostatitis is characterised by recurrent urinary tract infections or infection in the prostate with the same bacterial strain, which often results from urinary tract instrumentation. However, the cause and natural history of CPPS are unknown and not associated with active infection.

FOCUS OF THE REVIEW

CBP and CPPS can often be confusing for practitioners to manage given the disparate presentation of men's symptoms. This overview attempts to clarify and inform current management based on the most current literature. It is important to recognise that these two topics are distinctly different clinical, microbiological, and therapeutic entities.

COMMENTS ON EVIDENCE

There were 33 studies included in this overview, some of which are case-control studies. No placebo-controlled studies were found; however, control groups are probably unnecessary to evaluate the efficacy of antibiotics in CBP, as would be the case in other fields.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this overview was carried out from the date of the last search, August 2010, to February 2014. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 131 studies. After deduplication and removal of conference abstracts, 67 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 51 studies and the further review of 16 full publications. Of the 16 full articles evaluated, three systematic reviews and one RCT were included at this update.

ADDITIONAL INFORMATION

Although there are no placebo-controlled studies, it is well established that appropriate antibiotic treatment for CBP is associated with improved outcomes in terms of elimination of infection from the prostate and ancillary cystitis or other related symptoms. CPPS is a syndrome with an unclear aetiology that does not have any effective treatments. Chronic abacterial prostatitis is another term for CPPS; however, it is inaccurate as bacteria not responsible for the symptoms may occasionally be localised in the prostate. It is possible, but there is currently no evidence that an infection leads to the syndrome.

DEFINITION

Chronic bacterial prostatitis (CBP) is characterised by recurrent infections with documented positive cultures of expressed prostatic secretions. It is asymptomatic until the patient has a urinary tract infection with associated symptoms such as suprapubic, lower back, or perineal pain, with or without mild urgency and increased frequency of urination and dysuria. However, it will be asymptomatic between acute infective episodes. **Chronic pelvic pain syndrome (CPPS)** is characterised by pelvic or perineal pain in the absence of pathogenic bacteria in expressed prostatic secretions. It is often associated with irritative and obstructive voiding symptoms including urgency, frequency, hesitancy, and poor interrupted flow. Symptoms can also include pain in the suprapubic region, lower back, penis, testes, or scrotum and painful ejaculation. CPPS may be inflammatory (white cells present in prostatic secretions) or non-inflammatory (white cells absent in prostatic secretions). [1] A classification system for the prostatitis syndromes has been developed by the US National Institutes of Health (NIH). [2]

INCIDENCE/ PREVALENCE

One community-based study in the US (cohort of 2115 men aged 40–79 years) estimated that 9% of men have a diagnosis of either type of prostatitis at any one time. [3] Another observational study found that, in men presenting with genito-urinary symptoms, 8% of those presenting to urologists and 1% of those presenting to primary-care physicians were diagnosed as having CBP or CPPS. [4] However, most cases were abacterial; therefore, these studies are generally examining the

prevalence of CPPS (formerly known as 'abacterial prostatitis'). CBP, although easy to diagnose, is rare.

AETIOLOGY/ RISK FACTORS

Organisms commonly implicated in bacterial prostatitis include *Escherichia coli*, other gram-negative enterobacteriaceae, occasionally *Pseudomonas* species, and, rarely, gram-positive enterococci. Risk factors for chronic bacterial prostatitis include urethral catheterisation or instrumentation, condom drainage, dysfunctional voiding (high-pressure urination), and unprotected anal intercourse. The cause of CPPS is unclear, although it has been suggested that it may be caused by undocumented infections with *Chlamydia trachomatis*, [5] *Ureaplasma urealyticum*, [6] *Mycoplasma hominis*, [7] and *Trichomonas vaginalis*. [8] Viruses, [9] [10] *Candida* (in immunosuppressed people), [11] and parasites [12] have also rarely been implicated. Non-infectious factors might also be involved, including inflammation, [13] autoimmunity, [14] hormonal imbalances, [15] pelvic floor tension myalgia, [16] intraprostatic urinary reflux, [17] and psychological disturbances. [18] In one case-control study (463 men with CPPS; 121 asymptomatic age-matched controls), when compared with controls, men with CPPS reported a significantly higher lifetime prevalence of non-specific urethritis; CVD; neurological disease; psychiatric conditions; and haematopoietic, lymphatic, or infectious disease (non-specific urethritis: 12% with CPPS *v* 4% with no CPPS; P = 0.008; CVD: 11% with CPPS *v* 2% with no CPPS; P = 0.004; neurological disease: 41% with CPPS *v* 14% with no CPPS; P <0.001; psychiatric conditions: 29% with CPPS *v* 11% with no CPPS; P <0.001; haematopoietic, lymphatic, or infectious disease: 41% with CPPS *v* 20% with no CPPS; P <0.001). [19] Further studies are necessary to determine whether these factors play a role in the pathogenesis of CPPS. [19]

PROGNOSIS

The natural histories of untreated CBP and CPPS remain ill-defined. CBP usually causes recurrent UTI in men, whereas CPPS does not. [20] Several investigators have reported an association between CBP, CPPS, and infertility. [21] One study found that CPPS had an impact on quality of life similar to that of angina, Crohn's disease, or a previous MI. [22]

AIMS OF INTERVENTION

The aims of intervention are different and depend on the disease process. In CBP, the aim is to eliminate bacteria from the prostate, resulting in no further UTIs, with minimum adverse effects. In CPPS, the aim is clinically significant improvement in symptoms with minimum adverse effects.

OUTCOMES

Symptom improvement (includes rates of clinical cure/clinical success, symptom scores, bother scores, and urodynamics; does not include bacteriological cure rate); **bacteriological cure rate** (for chronic bacterial prostatitis question only); clearance of previously documented organisms from prostatic secretions, microbiological eradication rates, negative bacterial culture; **recurrence rate**; **quality of life**; **adverse effects**.

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal February 2014. Databases used to identify studies for this systematic review include: Medline 1966 to February 2014, Embase 1980 to February 2014, The Cochrane Database of Systematic Reviews 2014, issue 1 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this review were systematic reviews and RCTs published in English, at least single-blinded, and containing 20 or more individuals (10 in each arm), of whom more than 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed a priori with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our predefined criteria for inclusion in the benefits and harms section, may have been reported in the 'Further information on studies' or 'Comment' section. **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically

search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Data and quality** To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 29). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of treatments for chronic bacterial prostatitis?

OPTION ANTIMICROBIAL DRUGS (ORAL) FOR CBP

- For GRADE evaluation of interventions for Chronic bacterial prostatitis and chronic pelvic pain syndrome, see table, p 29 .
- Oral antimicrobial drugs are beneficial in men with CBP, although studies comparing them with placebo or no treatment have not been found.
- Clinical success rates with oral antimicrobials have reached about 70% to 90% at 6 months in studies comparing different regimens.
- Antimicrobial selection must be appropriate for the person. Appropriate selection includes: a person with a documented infection on localisation culture, bacteria that are susceptible to the therapy, and an antimicrobial that can penetrate the prostate. However, despite this there will still be some treatment failure due to sequestration of bacteria within the prostate.
- Trimethoprim-sulfamethoxazole (co-trimoxazole) and quinolones are most commonly used.

Benefits and harms

Oral antimicrobial drugs versus placebo or no antimicrobial drugs:

We found one systematic review (search date 2012), [23] which identified no RCTs.

Oral antimicrobial drugs versus each other:

We found one systematic review (search date 2012), [23] which included participants with category II National Institute of Diabetes and Digestive and Kidney Diseases (NIH-NIDDK) consensus definition of chronic bacterial prostatitis, or chronic bacterial prostatitis according to an earlier definition (pathogenic bacteria recovered in significant numbers from a purulent prostatic fluid in the absence of concomitant urinary tract infection or significant signs). Many of the included RCTs were open-label, which was outside the inclusion criteria of this overview. The review [23] included two double-blind RCTs [24] [25] of sufficient quality, which we have reported directly from the original RCT reports. The review reported pooled data for bacteriological cure, which we have also reported. [23]

Symptom improvement

Oral antimicrobial drugs compared with each other We don't know whether levofloxacin and ciprofloxacin differ in effectiveness at improving clinical success rates (defined as complete resolution of symptoms, improvement in symptoms, or clear improvement without need for additional antimicrobial drugs), or whether levofloxacin and prulifloxacin differ in effectiveness at improving symptoms (measured by NIH-CPSI scores) at 6 months in men with chronic bacterial prostatitis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical success					
[24] RCT	377 men with chronic bacterial prostatitis In review [23]	**Clinical success , 6 months** 102/136 (75%) with levofloxacin for 28 days 91/125 (73%) with ciprofloxacin for 28 days Clinical success was defined as complete resolution of symptoms or clear improvement without need for additional antimicrobial drugs Based on 261 people with a pathogen identified at admission and who were microbiologically assessable	Difference –2.2% 95% CI –13.3% to +8.9%	⟷	Not significant
[25] RCT	96 men with chronic bacterial prostatitis In review [23]	**Mean decrease in National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) score , 6 months after treatment completion** 10.75 with prulifloxacin for 4 weeks 10.73 with levofloxacin for 4 weeks	P = 0.98	⟷	Not significant

Bacteriological cure rate

Oral antimicrobial drugs compared with each other We don't know whether levofloxacin and other fluoroquinolones (ciprofloxacin and prulifloxacin combined in analysis) differ in effectiveness at improving microbiological eradication rates in men with chronic bacterial prostatitis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Bacteriological cure					
[23] Systematic review	Men with chronic bacterial prostatitis 2 RCTs in this analysis	**Pathogen eradication** 134/181 (74%) with levofloxacin for 28 days 128/169 (76%) with other fluoroquinolone (ciprofloxacin/prulifloxacin) for 28 days	RR 0.98 95% CI 0.87 to 1.10 P = 0.7	⟷	Not significant

Recurrence rate

No data from the following reference on this outcome. [24] [25]

Quality of life

No data from the following reference on this outcome. [24] [25]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[24] RCT	377 men with chronic bacterial prostatitis In review [23]	**At least 1 treatment-related adverse effect** 87/197 (44%) with levofloxacin for 28 days 67/180 (37%) with ciprofloxacin for 28 days Gastrointestinal disorders were the most common adverse effects associated with both treatments	Significance not assessed		
[24] RCT	377 men with chronic bacterial prostatitis In review [23]	**Gastrointestinal disturbances** 19% with levofloxacin for 28 days 17% with ciprofloxacin for 28 days Absolute numbers not reported Gastrointestinal disorders were the most common adverse effects associated with both treatments	Significance not assessed		
[25] RCT	96 men with chronic bacterial prostatitis In review [23]	**Adverse effects , 6 months after treatment completion** 8/44 (18%) with prulifloxacin for 4 weeks 10/45 (22%) with levofloxacin for 4 weeks Adverse effects were mostly minor in nature (diarrhoea, skin rash, gastric pain, headache, nausea), although 1 person in the levofloxacin group withdrew from the study owing to gastric pain	P = 0.79	⟷	Not significant

Further information on studies

[23] The review reported that both double-blind RCTs were at high risk of reporting bias, the level of blinding of outcome assessment was unclear in both, and in one RCT it was unclear whether allocation was concealed or not.

Comment: We found data from retrospective case series about the bacteriological cure rates of different antimicrobials. [26] [27] [28] These data do not compare antimicrobial drugs with placebo, no treatment, or other treatments.

Trimethoprim-sulfamethoxazole (co-trimoxazole)
One non-systematic review identified eight retrospective case series in 1140 men with bacteriologically confirmed prostatitis treated with trimethoprim-sulfamethoxazole (trimethoprim 160 mg plus sulfamethoxazole 800 mg twice daily for 10–140 days). [26] The studies reported cure rates of 0% to 71%. More than 30% of men were cured when treated for at least 90 days. The review did not report on adverse effects.

Quinolones
One non-systematic review summarised three retrospective case series in 106 men treated with norfloxacin (400 mg twice daily for 10, 28, and 174 days). [27] The studies reported cure rates of 64% to 88%.

Amoxicillin-clavulanic acid (co-amoxiclav) and clindamycin
One case series included 50 men resistant to empirical treatment with quinolones. [28] The expressed prostatic secretions from 24 of these men exhibited high colony counts of gram-positive and gram-negative anaerobic bacteria, either alone (18 men) or in combination with aerobic bacteria (6 men). After treatment with either amoxicillin-clavulanic acid or clindamycin for 3 to 6 weeks, all men had a decrease or total elimination of symptoms, and no anaerobic bacteria were detected in prostatic secretions. [28] Higher cure rates with quinolones may be explained by greater penetration into the prostate. [29] We reviewed only studies that used standard methods to localise infection to the prostate. [30]

Clinical guide
Most clinicians agree that antimicrobial drugs are the preferred treatment for chronic bacterial prostatitis. If the bacteria are susceptible to many antimicrobials, oral fluoroquinolones or trimethoprim are utilised as the drug must be absorbed by the prostate. However, if symptoms do not improve after eradication of bacteria, alternative treatments should be investigated.

OPTION ANTIMICROBIAL DRUGS (LOCALLY INJECTED) FOR CBP

- For GRADE evaluation of interventions for Chronic bacterial prostatitis and chronic pelvic pain syndrome, see table, p 29 .
- We don't know whether local injections of antimicrobial drugs improve symptoms compared with no treatment as we found no direct information from RCTs.

Benefits and harms

Local injection of antimicrobial drugs versus placebo or no antimicrobial drugs:

We found one systematic review (search date 2012), [23] which found no RCTs.

Local injection of antimicrobial drugs versus each other:

We found one systematic review (search date 2012), [23] which found no RCTs.

Comment:

We found one small RCT (50 men with prostatic secretions sensitive to amikacin) comparing anal submucosal injection of amikacin with intramuscular amikacin. [31] It found that anal submucosal injection significantly improved symptom score and bacteriological cure rate at 3 months compared with intramuscular injection (NIH-CPSI score: 9.0 with anal submucosal injection of amikacin daily for 10 days *v* 22.5 with intramuscular amikacin daily for 10 days; P <0.05; negative bacterial culture, 28/30 [93%] with anal submucosal injection of amikacin daily for 10 days *v* 7/20 [35%] with intramuscular amikacin daily for 10 days; P <0.05).

Another small cohort study (24 men with refractory chronic bacterial prostatitis) found that eradication of infection was eventually achieved, after an unstated period, in 15 men, with gentamicin 160 mg plus cefazolin 3 g injected directly into the prostate through the perineum. [32]

Clinical guide
There is limited evidence that local injection of antimicrobial drugs improves bacterial eradication rates compared with the standard treatment of oral antimicrobial drugs, and treatments of this type remain experimental. However, if first-line therapy for CBP with oral antimicrobial treatment fails, a local injection of antimicrobial therapy is reasonable. An additional advantage is that direct injection allows bypassing of the prostatic capsule and thus allows use of other antimicrobials. A third-line option is chronic oral antibiotic suppression to prevent recurrent cystitis. There is the potential for side effects with any medication, thus the risks of chronic antibiotic use (such as tendon damage with quinolones) must be weighed against the potential benefits. However, a chronic suppression approach only mandates adequate drug levels in the urine and does not require penetrance of the prostate, thus many antibiotic choices with a safer side effect profile are available, such as nitrofurantoin and cephalosporins.

OPTION TRANSURETHRAL RESECTION OF THE PROSTATE FOR CBP

- For GRADE evaluation of interventions for Chronic bacterial prostatitis and chronic pelvic pain syndrome, see table, p 29 .
- We found no direct information from RCTs about transurethral resection of the prostate in the treatment of men with chronic bacterial prostatitis.

Benefits and harms

Transurethral resection of the prostate (TURP):

We found no systematic review or RCTs on the effects of TURP in men with chronic bacterial prostatitis.

Comment:

One RCT in men with benign prostatic hypertrophy found no significant difference in the incidence of impotence or urinary incontinence between TURP and watchful waiting. [33]

One retrospective study reported 40% to 50% cure rates in 50 men with chronic prostatitis treated with TURP. However, proof of bacterial prostatitis was not obtained in many of the men. [34] According to current practice, there is a second-line role for local eradication of infected prostatic tissue by TURP in cases of failure of oral antimicrobials. A third-line option is chronic oral antibiotic suppression to prevent recurrent cystitis.

QUESTION What are the effects of treatments for chronic pelvic pain syndrome?

OPTION ALPHA-BLOCKERS FOR CPPS

- For GRADE evaluation of interventions for Chronic bacterial prostatitis and chronic pelvic pain syndrome, see table, p 29 .
- The effectiveness of alpha-blockers in people with CPPS is inconclusive; the data from RCTs fluctuate between effective and ineffective, most probably because of the heterogeneity of participants in the RCTs.

Benefits and harms

Alpha-blockers versus placebo:

We found two systematic reviews (search date 2010; [35] and 2011 [36]), which included slightly different RCTs, pooled data, and reported slightly different outcomes. We have, therefore, reported both reviews. The reviews included 10 RCTs in total. Both reviews included eight RCTs, six of which were common to both. Each review also included two RCTs not included in the other review. The second review included one RCT (151 men) published after the search date of the first review. We found one subsequent RCT, which compared tamsulosin with placebo for 6 months (see Further information on studies). [37]

Symptom improvement

Alpha-blockers compared with placebo Alpha-blockers may be more effective than placebo at improving symptom scores (including total symptom scores, pain, and voiding scores measured by NIH-CPSI, International Prostate Symptom Score (IPSS), or Prostatitis Symptom Score Index (PSSI) scales) in men with CPPS. However, there was considerable variation among RCTs, and the evidence was weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[35] Systematic review	Men with CPPS categories IIIA or IIIB, according to the NIH classification 5 RCTs in this analysis	**Mean total symptom score , end of treatment (assessed between 6–24 weeks)** with alpha blockers with placebo 568 men in this analysis	SMD –1.7 95% CI –0.6 to –2.8 The review reported that this was equivalent to –5.5 units, 95% CI –0.9 units to –10.0 units on NIH-CPSI or International Prostate Symptom Score (IPSS) scales	○○○	alpha blockers

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
			Significant heterogeneity in this analysis (I^2 96.4%; see Further information on studies) The review reported that minimal clinical difference for NIH-CPSI, IPSS, and Prostatitis Symptom Score Index (PSSI) scales were 3–6 points		
[35] Systematic review	Men with CPPS categories IIIA or IIIB, according to the NIH classification 6 RCTs in this analysis	**Mean pain score , end of treatment (assessed between 6–24 weeks)** with alpha blockers with placebo 637 men in this analysis	SMD –1.1 95% CI –0.3 to –1.8 Significant heterogeneity in this analysis (I^2 94%; see Further information on studies) The review reported that this was equivalent to 2.2 points on NIH-CPSI scale, and 1.9 points on PSSI/pain questionnaire (95% CI not reported)	○○○	alpha blockers
[35] Systematic review	Men with CPPS categories IIIA or IIIB according to the NIH classification 5 RCTs in this analysis	**Mean voiding score , end of treatment (assessed between 6–24 weeks)** with alpha blockers with placebo 568 men in this analysis	SMD –1.4 95% CI –0.5 to –2.3 See Further information on studies The review reported that this was equivalent to 3.1 units on the NIH-CPSI and IPSS scales (95% CI not reported)	○○○	alpha blockers
[35] Systematic review	Men with CPPS categories IIIA or IIIB according to the NIH classification 6 RCTs in this analysis	**Treatment response rate, various definitions used in different RCTs (e.g., 33% or 50% decrease in NIH-CPSI score, or 4-point decrease in NIH-CPSI from baseline) , treatment duration 6–24 weeks** with alpha blockers with placebo 602 men in this analysis	RR 1.6 95% CI 1.1 to 2.3 Heterogeneity I^2 64%, P value for heterogeneity not reported (may have been due in part to duration of treatment) Subgroup analysis by treatment duration was homogeneous (6–12 weeks' duration: RR 1.0, 95% CI 0.8 to 1.3; 14–24 weeks' duration: RR 2.0, 95% CI 1.4 to 3.0)	●○○	alpha blockers
[36] Systematic review	Men with NIH category III prostatitis 8 RCTs in this analysis	**Changes in NIH-CPSI total score , timescale not reported** with alpha blockers with placebo Absolute results reported graphically 770 men in this analysis	MD –4.80 95% CI –2.58 to –7.07 Significant heterogeneity (I^2 76%, P value for heterogeneity <0.0005; see Further information on studies)	○○○	alpha blockers
[36] Systematic review	Men with NIH category III prostatitis 8 RCTs in this analysis	**Changes in NIH-CPSI pain domain subscore , timescale not reported** with alpha blockers with placebo Absolute results reported graphically 761 men in this analysis	MD –2.1 95% CI –1.2 to –3.1 Significant heterogeneity (I^2 62%, P value for heterogeneity = 0.01; see Further information on studies)	○○○	alpha blockers
[36] Systematic review	Men with NIH category III prostatitis 7 RCTs in this analysis	**Changes in NIH-CPSI voiding domain subscore , timescale not reported**	MD –1.06 95% CI –0.39 to –1.73	○○○	alpha blockers

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with alpha blockers with placebo Absolute results reported graphically 724 men in this analysis	Significant heterogeneity (I^2 66%, P value for heterogeneity = 0.007 (see Further information on studies)		
[36] Systematic review	Men with NIH category III prostatitis Number of RCTs included in analysis not reported	**Global improvement (outcome not further defined) , timescale not reported** with alpha blockers with placebo Absolute results not reported	RR 1.1 95% CI 0.86 to 1.39 Significant heterogeneity (I^2 56%, P value for heterogeneity <0.005; see Further information on studies)	⟷	Not significant
[37] RCT	100 men aged 20–45 years, with CPPS NIH category IIIA or IIIB, pain or discomfort for at least 3 months	**Change in total NIH-CPSI score , 6 months** 7.5 with tamsulosin 4.0 with placebo Result based on 93 people	P <0.01 The difference between groups was also significant at 3 months (P <0.001)	○○○	tamsulosin
[37] RCT	100 men aged 20–45 years, with CPPS NIH category IIIA or IIIB, pain or discomfort for at least 3 months	**Change in total NIH-CPSI score , 12 months** 6.2 with tamsulosin 3.8 with placebo Result based on 92 people	Reported as not significant P value not reported The difference between groups was also not significant at 18 months (P value not reported)	⟷	Not significant
[37] RCT	100 men aged 20 to 45 years, with CPPS NIH category IIIA or IIIB, pain or discomfort for at least 3 months	**Change in pain domain score of NIH-CPSI score , 12 months** 3.4 with tamsulosin 1.5 with placebo Result based on 92 people	Reported as not significant P value not reported	⟷	Not significant
[37] RCT	100 men aged 20 to 45 years, with CPPS NIH category IIIA or IIIB, pain or discomfort for at least 3 months	**Change in urinary domain score of NIH-CPSI score , 12 months** 1.4 with tamsulosin 1.2 with placebo Result based on 92 people	Reported as not significant P value not reported	⟷	Not significant
[37] RCT	100 men aged 20–45 years, with CPPS NIH category IIIA or IIIB, pain or discomfort for at least 3 months	**Responders (having a 4-point or more decrease in NIH-CPSI total score) , 12 months** 30/45 (67%) with tamsulosin 20/47 (43%) with placebo	P <0.05 The difference between groups was also significant at 3 months (P <0.05) and 6 months (P <0.05), but not at 18 months (P >0.05)	○○○	tamsulosin

Recurrence rate

No data from the following reference on this outcome. [35] [36] [37]

Quality of life

Alpha-blockers compared with placebo Alpha-blockers may be more effective than placebo at improving quality of life scores (measured by NIH-CPSI quality of life domain or IPSS scales) in men with CPPS. However, there was considerable variation among RCTs, and the evidence was weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[35] Systematic review	Men with CPPS categories IIIA or IIIB according to the NIH classification 5 RCTs in this analysis	**Mean quality of life score , end of treatment (assessed between 6 and 24 weeks)** with alpha blockers with placebo 568 men in this analysis	SMD –1.0 95% CI –0.2 to –1.8 Result was heterogeneous (test statistic not reported), funnel plot suggested publication bias from 2 small RCTs, and adjusting for this removed the significant benefit (P = 0.13) The review reported that this equates to about 1.4 units on the NIH-CPSI and IPSS scales (95% CI not reported)	○○○	alpha blockers
[36] Systematic review	Men with NIH category III prostatitis 7 RCTs in this analysis	**Changes in NIH-CPSI quality of life score , (timescale not reported)** with alpha blockers with placebo Absolute results reported graphically 770 men in this analysis	MD –1.37 95% CI –0.40 to –2.33 Significant heterogeneity (I^2 84%, P value for heterogeneity <0.0005; see Further information on studies)	○○○	alpha blockers
[37] RCT	100 men aged 20–45 years, with CPPS NIH category IIIA or IIIB, pain or discomfort for at least 3 months	**Changes in NIH-CPSI quality of life score , 6 months** 1.3 with tamsulosin 1.2 with placebo 93 men in this analysis	Reported as not significant P value not reported	⟷	Not significant
[37] RCT	100 men aged 20–45 years, with CPPS NIH category IIIA or IIIB, pain or discomfort for at least 3 months	**Changes in NIH-CPSI quality of life score , 12 months** 1.5 with tamsulosin 1.1 with placebo	Reported as not significant P value not reported	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[38] RCT **3-armed trial**	70 men with chronic abacterial prostatitis In review [35]	**Adverse effects** with alfuzosin for 6 months with placebo The RCT found no withdrawals due to adverse effects with any treatment 1 man (5%) experienced heartburn and 4 men (21%) experienced decreased ejaculate volume with alfuzosin 40 men in this analysis 30 men who did not wish to be entered into the randomisation received standard treatment The remaining arm evaluated standard treatment (hot sitz baths plus anti-inflammatory drugs)			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[39] RCT	86 men with chronic abacterial prostatitis In review [35]	**Treatment-related adverse effects , 14 weeks** 18/43 (42%) with terazosin 9/43 (21%) with placebo	P = 0.04	○○○	placebo
[39] RCT	86 men with chronic abacterial prostatitis In review [35]	**Dizziness , 14 weeks** 7/43 (16%) with terazosin 2/43 (5%) with placebo One of the most commonly reported adverse effects	Significance not assessed		
[39] RCT	86 men with chronic abacterial prostatitis In review [35]	**Asthenia , 14 weeks** 7/43 (16%) with terazosin 3/43 (7%) with placebo One of the most commonly reported adverse effects	Significance not assessed		
[40] RCT **3-armed trial**	90 men with chronic abacterial prostatitis In review [35] Quasi-randomised RCT; men were randomised in the order they appeared	**Adverse effects** 12/30 (40%) with doxazosin 7/30 (23%) with placebo 60 men in this analysis (30 men in the doxazosin group and 30 in the placebo group) The third arm assessed a triple therapy (doxazosin plus ibuprofen plus muscle relaxant therapy); this intervention is not covered by this overview and the results from this arm are not reported here	Significance not assessed		
[40] **3-armed trial**	90 men with chronic abacterial prostatitis In review [35] Quasi-randomised trial; men were randomised in the order they appeared	**Dizziness** 3/30 (10%) with doxazosin 2/30 (7%) with placebo 60 men in this analysis (30 men in the doxazosin group and 30 in the placebo group) The third arm assessed a triple therapy (doxazosin plus ibuprofen plus muscle relaxant therapy); this intervention is not covered by this overview and the results from this arm are not reported here	Significance not assessed		
[40] RCT **3-armed trial**	90 men with chronic abacterial prostatitis In review [35] Quasi-randomised trial; men were randomised in the order they appeared	**Postural hypotension** 3/30 (10%) with doxazosin 1/30 (3%) with placebo 60 men in this analysis (30 men in the doxazosin group and 30 in the placebo group) The third arm assessed a triple therapy (doxazosin plus ibuprofen plus muscle relaxant therapy); this intervention is not covered by this review and the results from this arm are not reported here	Significance not assessed		
[40] RCT	90 men with chronic abacterial prostatitis	**Gastrointestinal complaints**	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
3-armed trial	In review [35] Quasi-randomised trial; men were randomised in the order they appeared	2/30 (7%) with doxazosin 2/30 (7%) with placebo 60 men in this analysis (30 men in the doxazosin group and 30 in the placebo group) The third arm assessed a triple therapy (doxazosin plus ibuprofen plus muscle relaxant therapy); this intervention is not covered by this review and the results from this arm are not reported here			
[41] RCT **4-armed trial**	196 men with chronic abacterial prostatitis In review [35] 2 × 2 factorial design	**Adverse effects** with tamsulosin with no tamsulosin Absolute results not reported The 4 arms evaluated ciprofloxacin, tamsulosin (an alpha-blocker), combination therapy (ciprofloxacin plus tamsulosin), and placebo The RCT found no significant difference in the incidence of adverse effects (mostly gastrointestinal disturbances) between groups	P >0.2	⟷	Not significant
[42] RCT	272 men with prostatitis for at least 2 years, and with no previous treatment with an alpha-blocker In review [35]	**Adverse effects** 38/138 (28%) with alfuzosin 39/134 (29%) with placebo The most commonly reported adverse effect was pain, and the body system most commonly affected by adverse effects was the gastrointestinal system	P = 0.79	⟷	Not significant
[37] RCT	100 men aged 20–45 years, with CPPS NIH category IIIA or IIIB, pain or discomfort for at least 3 months	**Adverse effects** with tamsulosion with placebo 13 people with tamsulosion and two people with placebo had adverse effects, most of which were classified as mild or moderate Two people with tamsulosin and one with placebo withdrew because of adverse effects (further details not reported)			

No data from the following reference on this outcome. [35] [36]

Alpha-blockers versus each other:

We found no systematic review or RCTs of sufficient quality (see comment).

Further information on studies

[35] *Heterogeneity* For total symptom scores, the review reported that meta-regression did not identify the source of heterogeneity. Sensitivity analysis using four 'higher-quality' RCTs did not affect the significance of the result, the Eggar test indicated publication bias (P = 0.03), and an analysis adjusted for possible publication bias resulted in no evidence of treatment benefit (P = 0.39). For the pain analysis, sensitivity analysis using four 'higher-quality' RCTs did not affect the significance of the result, the Eggar test suggested publication bias due to small study effect (P = 0.02), and an analysis adjusted for possible publication bias resulted in no evidence of treatment benefit (P = 0.06). For voiding scores, the heterogeneity test statistic was not reported. Sensitivity analysis using four 'higher-quality' RCTs did not affect the significance of the result, the Eggar test suggested publication bias due to small study effect (P = 0.02), and an analysis adjusted for possible publication bias resulted in no evidence of treatment benefit (P = 0.10). *Methods* Of the eight included RCTs, three had unclear sequence generation and six had unclear allocation concealment.

[36] *Heterogeneity* The review reported that it found no evidence of publication bias in NIH-CPSI total score, pain, voiding, or quality of life analyses. It reported that factors influencing the heterogeneity included inadequate sequence generation, lack of concealed allocation, study duration, and requiring an NIH-CPSI cut-off score for study entry.

[37] The RCT noted that there were no significant differences between groups in peak urinary flow, post-voiding residual volume, and International Index of Erectile Function (IIEF) over the course of the trial. It noted that the dose of tamsulosin commonly used in China and used in the trial was lower than that used in other countries, and the results might be different with different drug dosages and in different populations.

Comment:

The first review [35] reported that, although alpha-blockers improved outcomes, the magnitudes of treatment effects are distorted by publication bias and small study effects. It noted that some RCTs were unclear in randomisation sequence generation; hence, selection bias or confounding might be present. The second review [36] noted variability in the entry criteria for RCTs, potential effects of age (above or less than 50 years), whether men were alpha-blocker naïve, variations in study quality, and that placebo effects needed to be taken into account in interpreting results. It observed that the variability in response could suggest that CPPS is actually comprised of a number of separate disease entities with discrete causes that require different treatments. [36]

Alpha-blockers versus placebo

The largest randomised, multi-centre, double-blind, placebo-controlled trial to date showed no overall difference between placebo and alpha-blocker therapy (alfuzosin 10 mg/day). Both groups showed a similar response rate, defined as a decrease of four or more points on the NIH-CPSI of 49% at 12 weeks. [42] Other trials looked at response periods greater than 3 months; thus, it is difficult to generalise the results to longer periods of treatment. Additionally, people with a lower urinary tract symptoms (LUTS) component may be a subgroup that would benefit, although the literature does not currently support this premise.

Alpha-blockers versus each other or versus antimicrobials

We found one five-armed open-label RCT that did not meet the inclusion criteria for *BMJ Clinical Evidence*. [43] The RCT divided participants into groups depending on prostatitis type (IIIA or IIIB), and randomly allocated them to treatment with either tamsulosin, treatment with a combination of tamsulosin plus levofloxacin, or, for only the people with type IIIA disease, levofloxacin alone. All groups had a decrease in symptom scores, but improvements in symptom scores in the combined treatment group were superior to those in the single treatment groups. Combination therapy improved pain, urinary symptoms, and quality-of-life scores compared with levofloxacin alone (P <0.05). The authors conclude that tamsulosin and levofloxacin are both effective in the treatment of, and may have an additional effect in, the treatment of non-bacterial prostatitis.

Drug safety alert (August 2007)

A drug safety alert has been issued on risk of intra-operative floppy iris syndrome during cataract surgery with tamsulosin (https://www.gov.uk/drug-safety-update/-1-adrenoreceptor-antagonists-intraoperative-floppy-iris-syndrome-ifis).

Clinical guide

Many clinicians believe that alpha-blockers are the appropriate first-line treatment for CPPS, despite the lack of strong RCT evidence. Clinical practice suggests that alpha-blockers may help some and not others within the CPPS syndrome, due to the heterogeneity of the patient population. With a low side effect profile, it is an appropriate first-line therapy even despite the lack of strong RCT evidence. However, if alpha-blockers fail to improve symptoms, as determined by the NIH-CPSI, alternative treatments should be investigated. Although one trial suggested efficacy with a combi-

nation of alpha-blocker and antimicrobial, in the absence of robust evidence the clinician must weigh the potential harm (i.e., side effect profile of ciprofloxacin) with the small potential for benefit.

OPTION 5 ALPHA-REDUCTASE INHIBITORS FOR CPPS

- For GRADE evaluation of interventions for Chronic bacterial prostatitis and chronic pelvic pain syndrome, see table, p 29 .
- We don't know whether 5 alpha-reductase inhibitors reduce symptoms in men with CPPS.

Benefits and harms

5 alpha-reductase inhibitors versus placebo:

We found one systematic review (search date 2010), [35] which identified two RCTs. [44] [45] We have reported the RCTs directly from their original reports.

Symptom improvement

5 alpha-reductase inhibitors compared with placebo We don't know whether finasteride is more effective than placebo at improving symptoms in men with CPPS (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[44] RCT	41 men In review [35]	**Symptom scores , 1 year** with finasteride with placebo Absolute results reported graphically 31/41 (75%) of men allocated to finasteride *v* 10/41 (25%) of men allocated to placebo	Reported as significant P value not reported The RCT was small and had low power (3:1 randomisation)	○○○	finasteride
[44] RCT	41 men In review [35]	**Pain , 1 year** with finasteride with placebo Absolute results not reported 31/41 (75%) of men allocated to finasteride *v* 10/41 (25%) of men allocated to placebo	Reported as not significant P value not reported The RCT was small and had low power (3:1 randomisation)	⟷	Not significant
[45] RCT	64 men In review [35]	**Treatment response (defined as >25% improvement in National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI scores) , 6 months** 33% with finasteride 16% with placebo Absolute numbers not reported	P >0.05	⟷	Not significant

Recurrence rate

No data from the following reference on this outcome. [35] [44] [45]

Quality of life

No data from the following reference on this outcome. [35] [44] [45]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[44] RCT	41 men In review [35]	**Partial impotence** 3/31 (10%) with finasteride 0/10 (0%) with placebo 31/41 (75%) of men allocated to finasteride *v* 10/41 (25%) of men allocated to placebo	Significance not assessed The RCT was small and had low power (3:1 randomisation)		
[45] RCT	64 men In review [35]	**Adverse effects** 5/33 (15%) with finasteride 7/31 (23%) with placebo	Significance not assessed		

Comment: Finasteride is known to decrease prostate volume (as it did in the study included in the review; P <0.03), but it is unclear how this relates to symptoms of prostatitis. [44]

Clinical guide
If alpha-blockers fail to provide symptom relief in men with CPPS, some physicians believe that 5 alpha-reductase inhibitors can be considered as a second-line treatment.

OPTION ALLOPURINOL FOR CPPS

- For GRADE evaluation of interventions for Chronic bacterial prostatitis and chronic pelvic pain syndrome, see table, p 29 .
- We don't know whether allopurinol reduces symptoms in men with CPPS.

Benefits and harms

Allopurinol versus placebo:

We found one systematic review (search date 2000, 1 RCT [46]). [47]

Symptom improvement

Allopurinol compared with placebo Allopurinol may be more effective than placebo at reducing symptoms (measured by an unvalidated 'degree of discomfort' score) in men with CPPS (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Degree of discomfort					
[46] RCT	54 men In review [47]	**Degree of discomfort score , 240 days** –1.1 with allopurinol 300 and 600 mg combined +0.2 with placebo The symptom score was not validated	P = 0.02	◌◌◌	allopurinol

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Rate of withdrawal was high (see Further information on studies for full details)			

Recurrence rate

No data from the following reference on this outcome. [47]

Quality of life

No data from the following reference on this outcome. [47]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[46] RCT	54 men In review [47]	**Adverse effects** with allopurinol 300 and 600 mg combined with placebo None of the men receiving allopurinol reported any significant adverse effects, but the RCT did not explain what constituted a significant adverse effect Rate of withdrawal was high (see Further information on studies for full details)			

Further information on studies

[46] In the RCT, 34 men (63%) completed the study; 55% of people on placebo and 68% of people on allopurinol completed the trial.

Comment: **Clinical guide**
If alpha-blockers fail to provide symptom relief in men with CPPS, some physicians believe that allopurinol can be considered as a second-line treatment.

OPTION MEPARTRICIN FOR CPPS

- For GRADE evaluation of interventions for Chronic bacterial prostatitis and chronic pelvic pain syndrome, see table, p 29 .
- We don't know whether mepartricin reduces symptoms in men with CPPS.

Benefits and harms

Mepartricin versus placebo:

We found one systematic review (search date 2011), [36] which identified one RCT. [48] We have reported the RCT directly from its original report.

Symptom improvement

Mepartricin compared with placebo We don't know whether oral mepartricin is more effective than placebo at improving symptoms in men with CPPS (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[48] RCT	26 men In review [36]	**Median score improvement in the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) for pain** –7 with mepartricin –2 with placebo	P = 0.009	○○○	mepartricin
[48] RCT	26 men In review [36]	**Median score improvement in the total NIH-CPSI score** –15 with mepartricin –5 with placebo	P = 0.0018	○○○	mepartricin
[48] RCT	26 men In review [36]	**Median score improvement in the NIH-CPSI for urinary dys-function** –5 with mepartricin –4 with placebo	P = 0.2891	⟷	Not significant

Recurrence rate

No data from the following reference on this outcome. [36] [48]

Quality of life

Mepartricin compared with placebo Oral mepartricin may be more effective than placebo at improving quality of life (measured by NIH-CPSI) in men with CPPS (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[48] RCT	26 men In review [36]	**Median score improvement in the NIH-CPSI for quality of life** –5 with mepartricin –1 with placebo	P = 0.0046	○○○	mepartricin

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[48] RCT	26 men In review [36]	**Adverse effects** with mepartricin with placebo The RCT found 2 cases of mild epigastric pain and nausea; however, no one discontinued treatment because of adverse effects			

Further information on studies

[36] The review noted that the RCT [48] had unclear allocation concealment and inadequate blinding.

Comment: Mepartricin has been shown to form a complex with oestrogen when taken orally, leading to faecal oestrogen excretion and lower plasma oestrogen levels.

Clinical guide
Mepartricin remains an experimental drug, but some physicians believe that it should be considered as a second-line treatment if alpha-blockers fail to provide symptomatic relief.

OPTION NON-STEROIDAL ANTI-INFLAMMATORY DRUGS FOR CHRONIC PELVIC PAIN SYNDROME

- For GRADE evaluation of interventions for Chronic bacterial prostatitis and chronic pelvic pain syndrome, see table, p 29 .
- We don't know whether Non-steroidal anti-inflammatory drugs (NSAIDs) are more effective than placebo in reducing symptoms in men with CPPS.

Benefits and harms

NSAIDs versus placebo:

We found two systematic reviews (search date 2010 [35] and search date 2011 [36]), which identified two RCTs. [49] [50] One RCT examined the effects of rofecoxib, which we have not reported further (see Comment). [50] The other RCT compared celecoxib with placebo. [49]

Symptom improvement

NSAIDs compared with placebo We don't know whether celecoxib is more effective than placebo at improving symptoms in men with CPPS (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[36] Systematic review	64 men with NIH category IIIA chronic pelvic pain syndrome Data from 1 RCT	**Mean changes in NIH-CPSI total score , timeframe not reported** 23.3 with celecoxib 24.7 with placebo	MD –1.40 95% CI –0.62 to –2.18	○○○	celecoxib
[36] Systematic review	64 men with NIH category IIIA chronic pelvic pain syndrome	**Mean changes in NIH-CPSI pain domain score , timeframe not reported** 10.1 with celecoxib	MD –1.00 95% CI –2.27 to +0.27	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Data from 1 RCT	11.1 with placebo			
[36] Systematic review	64 men with NIH category IIIA chronic pelvic pain syndrome Data from 1 RCT	**Mean changes in NIH-CPSI voiding domain score , time-frame not reported** 4.9 with celecoxib 4.8 with placebo	MD +0.10 95% CI –0.54 to +0.74	⟷	Not significant

Recurrence rate

No data from the following reference on this outcome. [36] [49]

Quality of life

No data from the following reference on this outcome. [36] [49]

Adverse effects

No data from the following reference on this outcome. [36] [49]

Comment: One of the reviews we found [35] identified one RCT of sufficient quality comparing rofecoxib (a COX-2 inhibitor) with placebo in men with CPPS. [50] However, rofecoxib has now been withdrawn from clinical use, so we have not reported it further.

OPTION PENTOSAN POLYSULFATE FOR CPPS

- For GRADE evaluation of interventions for Chronic bacterial prostatitis and chronic pelvic pain syndrome, see table, p 29 .
- We don't know whether pentosan polysulfate reduces symptoms in men with CPPS.

Benefits and harms

Pentosan polysulfate versus placebo:

We found two systematic reviews (search date 2010; [35] and 2011 [36]), which identified one RCT. [51] We found one additional RCT. [52] We have reported the RCTs directly from the original reports. [51] [52]

Symptom improvement

Pentosan polysulfate compared with placebo Pentosan polysulfate may be more effective than placebo at improving symptom scores in men with chronic pelvic pain syndrome (CPPS) (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[52] RCT	30 men	**Physician-rated improvement , 3 months** 7/10 (70%) with pentosan polysulfate sodium 5/14 (36%) with placebo 'Physician-rated improvement' is not an objective measurement (see Further information on studies for details on standard outcomes) Analysis was not by intention to treat (see Further information on studies)	RR 2.00 95% CI 0.87 to 4.40 The RCT may have been too small to detect important clinical differences between groups	⟷	Not significant
[52] RCT	30 men	**Proportion of people reporting improvement in symptom score , 3 months** 5/10 (50%) with pentosan polysulfate sodium 6/14 (43%) with placebo Analysis was not by intention to treat (see Further information on studies)	RR 1.2 95% CI 0.5 to 2.8	⟷	Not significant
[51] RCT	100 men In review [35] [36]	**Mean score improvement in the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) total score , 16 weeks** 5.9 with pentosan polysulfate 3.2 with placebo	P = 0.081	⟷	Not significant
[51] RCT	100 men In review [35] [36]	**Mean score improvement in the NIH-CPSI score for urinary symptoms domain , 16 weeks** 1.2 with pentosan polysulfate 0.5 with placebo	P = 0.374	⟷	Not significant
[51] RCT	100 men In review [35] [36]	**Mean score improvement in the NIH-CPSI score for pain domain , 16 weeks** 2.7 with pentosan polysulfate 1.7 with placebo	P = 0.21	⟷	Not significant

Recurrence rate

No data from the following reference on this outcome. [35] [36] [51] [52]

Quality of life

Pentosan polysulfate compared with placebo Pentosan polysulfate may be more effective than placebo at improving quality of life (measured by NIH-CPSI life quality domain score) in men with CPPS. However, the results varied by the analysis undertaken (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[51] RCT	100 men In review [35] [36]	**Mean score improvement in the NIH-CPSI score for life quality domain , 16 weeks** 2.0 with pentosan polysulfate 1.0 with placebo	P = 0.031 One review reported a further analysis of NIH-CPSI QoL score from this RCT, which found no significant difference between groups (100 men, timescale not reported: mean changes, 6.9 with pentosan polysulfate *v* 7.5 with placebo, mean difference –0.60, 95% CI –1.50 to +0.30)	○○○	pentosan polysulfate

No data from the following reference on this outcome. [52]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[52] RCT	30 men	**Adverse effects** with pentosan polysulfate sodium with placebo The RCT found that 2 men given pentosan polysulfate sodium reported diarrhoea; none of the men treated with placebo developed adverse gastrointestinal disturbances Analysis was not by intention to treat (see Further information on studies)			
[51] RCT	100 men In review [35] [36]	**Withdrawal because of adverse effects , 16 weeks** 11/51 (22%) with pentosan polysulfate 4/49 (8%) with placebo The most common adverse effects reported were diarrhoea, nausea, headache, abdominal pain, and back pain	Significance not assessed		
[51] RCT	100 men In review [35] [36]	**Diarrhoea , 16 weeks** with pentosan polysulfate with placebo	P >0.2	⟷	Not significant
[51] RCT	100 men In review [35] [36]	**Nausea , 16 weeks** with pentosan polysulfate with placebo	P >0.2	⟷	Not significant
[51] RCT	100 men In review [35] [36]	**Headache , 16 weeks** with pentosan polysulfate with placebo	P >0.2	⟷	Not significant
[51] RCT	100 men In review [35] [36]	**Abdominal pain , 16 weeks** with pentosan polysulfate	P >0.2	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with placebo			
[51] RCT	100 men In review [35] [36]	**Back pain , 16 weeks** with pentosan polysulfate with placebo	P >0.2	⟷	Not significant
[51] RCT	100 men In review [35] [36]	**Proportion of people with no adverse effects , after 16 weeks of treatment** with pentosan polysulfate with placebo Absolute results not reported	P = 1.0	⟷	Not significant

Further information on studies

[52] The RCT found no significant difference between pentosan polysulfate and placebo in other, more objective and standardised outcomes. The analysis in the RCT was not by intention to treat; six people were excluded from the analysis for non-compliance or because they had bacterial prostatitis.

Comment: None.

OPTION QUERCETIN FOR CPPS

- For GRADE evaluation of interventions for Chronic bacterial prostatitis and chronic pelvic pain syndrome, see table, p 29 .
- We don't know whether quercetin reduces symptoms in men with CPPS.

Benefits and harms

Quercetin versus placebo:

We found one systematic review (search date 2010), [35] which included one RCT. [53] We have reported that RCT from its original report.

Symptom improvement

Quercetin compared with placebo We don't know whether oral quercetin (a bioflavonoid) and placebo differ in effectiveness at improving symptoms in men with CPPS as we found insufficient evidence from one small RCT (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[53] RCT	33 men In review [35]	**Mean improvement in total National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) scores , 1 month** from 21 to 13 with quercetin from 20.2 to 18.8 with placebo	P = 0.003	○○○	quercetin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[53] RCT	33 men In review [35]	**Clinically meaningful improvement (more than 25% improvement in NIH-CPSI scores) , 1 month** 67% with quercetin 20% with placebo Absolute numbers not reported	P = 0.001	○○○	quercetin
[53] RCT	33 men In review [35]	**Urinary dysfunction , 1 month** with quercetin with placebo Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant

Recurrence rate

No data from the following reference on this outcome. [35] [53]

Quality of life

No data from the following reference on this outcome. [35] [53]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[53] RCT	33 men In review [35]	**Adverse effects** with quercetin with placebo 1 man reported headaches taking quercetin, and 1 man noted tingling of extremities No one stopped treatment because of adverse effects, and all symptoms resolved after cessation of treatment			

Comment: Despite lack of evidence, some physicians recommend a trial of quercetin, a naturally occurring bioflavinoid with antioxidant properties.

OPTION SITZ BATHS FOR CPPS

- For GRADE evaluation of interventions for Chronic bacterial prostatitis and chronic pelvic pain syndrome, see table, p 29 .
- We found no direct information from RCTs about sitz baths in the treatment of men with CPPS.

Benefits and harms

Sitz baths:

We found no systematic review or RCTs on the effects of sitz baths in men with CPPS.

Comment: None.

OPTION TRANSURETHRAL MICROWAVE THERMOTHERAPY FOR CPPS

- For GRADE evaluation of interventions for Chronic bacterial prostatitis and chronic pelvic pain syndrome, see table, p 29 .
- We don't know whether transurethral microwave thermotherapy (TUMT) reduces symptoms in men with CPPS.

Benefits and harms

Transurethral microwave thermotherapy versus sham treatment:

We found one systematic review (search date 1999, 1 double-blind RCT [54]). [55] The RCT included in the review compared TUMT with sham treatment. [54]

Symptom improvement

TUMT compared with sham treatment TUMT may be more effective than sham treatment at 21 months at increasing the proportion of men with an improvement of symptoms (measured by subjective global assessment) in men with CPPS. However, evidence was weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[54] RCT	20 men In review [55]	**Proportion of men with improvement of a subjective global assessment by >50% , mean of 21 months** 7/10 (70%) with TUMT 1/10 (10%) with sham treatment	Reported as significant P value not reported	◯◯◯	TUMT

Recurrence rate

No data from the following reference on this outcome. [55]

Quality of life

TUMT compared with sham treatment TUMT may be more effective than sham treatment at 3 months at improving quality of life (measured on a 10-point scale) in men with CPPS (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[54] RCT	20 men In review [55]	**Improvement in quality of life on a scale of 1–10 (lower score favourable) , 3 months** from 4.4 to 3.0 with TUMT from 5.2 to 5.2 with sham treatment	P <0.05	◯◯◯	TUMT

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[54] RCT	20 men In review [55]	**Adverse effects** with TUMT with sham treatment 4 men complained of transient (resolved in 3 weeks) adverse effects, including haematuria (2 men), UTI, impotence, urinary retention, urinary incontinence, and premature ejaculation (each occurring in 1 man) The RCT did not report on whether these men were treated with active or sham treatment			

Comment: TUMT caused persistent elevation of leukocytes in the prostatic fluid, which could indicate tissue damage.

GLOSSARY

Sitz bath A warm water bath taken in the sitting position. The water covers only the hips and buttocks.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

NIH classification system Category I: acute bacterial prostatitis is an acute infection of the prostate. Category II: chronic bacterial prostatitis is a recurrent infection of the prostate. Category III: chronic non-bacterial prostatitis/chronic pelvic pain syndrome (CP/CPPS) is where there is no demonstrable infection. Subgroups of this class are: (A) inflammatory CPPS (leukocytes seen in semen, prostatic fluid, or urine after prostatic massage); and (B) non-inflammatory CPPS (no leukocytes seen). Category IV: asymptomatic inflammatory prostatitis, no subjective symptoms but leukocytes found in prostate/prostatic secretions during work-up for other disorders (e.g., on prostate biopsy for prostate cancer). [2]

National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) Includes nine items across three domains: pain (4 items; 0–21), urinary symptoms (2 items; 0–10), and quality of life impact (3 items; 0–12). In all domains, higher scores indicate worse outcomes.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

5 alpha-reductase inhibitors for CPPS One systematic review added. [35] Categorisation unchanged (unknown effectiveness).

Alpha-blockers for CPPS Two systematic reviews added, [35] [36] and one subsquent RCT. [37] Categorisation unchanged (unknown effectiveness).

Antimicrobial drugs (locally injected) for CBP One systematic review added. [23] Categorisation unchanged (unknown effectiveness).

Mepartricin for CPPS One systematic review added. [36] Categorisation unchanged (unknown effectiveness).

NSAIDs for CPPS Two systematic reviews added. [35] [36] Categorisation unchanged (unknown effectiveness).

Pentosan polysulfate for CPPS Two systematic reviews added. [35] [36] Categorisation unchanged (unknown effectiveness).

Quercetin for CPPS One systematic review added. [35] Categorisation unchanged (unknown effectiveness).

Antimicrobial drugs (oral) for CBP One systematic review added. [23] Evidence re-evaluated. Categorisation changed from 'likely to be beneficial' to 'beneficial' (by consensus).

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Disclaimer

GRADE **Evaluation of interventions for Chronic bacterial prostatitis and chronic pelvic pain syndrome.**

Important outcomes			Bacteriological cure rate, Quality of life, Recurrence rate, Symptom improvement						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of treatments for chronic bacterial prostatitis?									
2 (357) [24] [25]	Symptom improvement	Oral antimicrobial drugs versus each other	4	–1	0	–1	0	Low	Quality point deducted for weak methods; directness point deducted for narrow range of comparators
2 (357) [24] [25]	Bacteriological cure rate	Oral antimicrobial drugs versus each other	4	–1	0	–1	0	Low	Quality point deducted for weak methods; directness point deducted for narrow range of comparators
What are the effects of treatments for chronic pelvic pain syndrome?									
at least 9 (at least 870) [35] [36] [37]	Symptom improvement	Alpha-blockers versus placebo	4	–1	–1	–1	0	Very low	Quality point deducted for weak methods; consistency point deducted for statistical heterogeneity; directness point deducted for possible publication bias
at least 8 (at least 870) [35] [36] [37]	Quality of life	Alpha-blockers versus placebo	4	–1	–1	–1	0	Very low	Quality point deducted for weak methods; consistency point deducted for statistical heterogeneity; directness point deducted for possible publication bias
2 (105) [44] [45]	Symptom improvement	5 alpha-reductase inhibitors versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (54) [46]	Symptom improvement	Allopurinol versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, poor follow-up, and incomplete definition of reported outcome
1 (26) [48]	Symptom improvement	Mepartricin versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and weak methods
1 (26) [48]	Quality of life	Mepartricin versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and weak methods
1 (64) [36] [49]	Symptom improvement	NSAIDs versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete recording of results; directness point deducted for data on only one NSAID
2 (124) [52] [51]	Symptom improvement	Pentosan polysulfate versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, no intention-to-treat analysis, and for subjective assessment of outcome
1 (100) [36] [51]	Quality of life	Pentosan polysulfate versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for significance of result dependent on statistical analysis performed
1 (33) [53]	Symptom improvement	Quercetin versus placebo	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; consistency point deducted for different results for different outcomes

Important outcomes	Bacteriological cure rate, Quality of life, Recurrence rate, Symptom improvement								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (20) [54]	Symptom improvement	Transurethral microwave thermotherapy versus sham treatment	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and subjective outcome measurement
1 (20) [54]	Quality of life	Transurethral microwave thermotherapy versus sham treatment	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and subjective outcome measurement

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.